REMARKS

Applicant appreciates the examination of the present application as evidenced by the final Office Action dated March 27, 2008 (hereinafter, the "Final Action."). Applicant respectfully submits that pending Claims 23, 26-35 and 45-83 are patentable for at least the reasons previously made of record[1] and further in view of the remarks set forth to address the issues presented in the Final Action.

I. Claim Rejections

In the Final Action, Claims 23, 26-35 and 45-83 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Dobbie "Separation of Peritoneal Surfaces Through the Maintenance of an Artificial Ascites as a Preventative of Peritoneal Adhesions." Abstract, 4th Peritoneum and Peritoneal Access Meeting, September 16-19, 1997 (hereinafter, "Dobbie") in view of U.S. Patent No. 4,886,789 to Milner (hereinafter, "Milner") or Treutner et al. "Prevention of Postoperative Adhesions by Single Intraperitoneal Medication," *Journal of Surgical Research* **59**: 764-771 (1995) (hereinafter, "Treutner"). *See* Final Office Action, page 2. Applicant respectfully disagrees with this assertion.

A. Dobbie in view of Milner

The Examiner maintains that Dobbie advocates use of an icodextrin solution not only as a peritoneal dialysate but as well for use post-operatively in patients with a high risk of abdominal adhesions, which motivates one to combine Dobbie with the teachings of Milner. *See* Final Action, page 3.

Dobbie does not make any mention of leaving the icodextrin solution in the cavity and indeed provides no guidance of how to apply icodextrin to a body cavity in a method to reduce adhesions. One of ordinary skill in the art would have been motivated by their knowledge of the principles of the dialysis technique, as reiterated in the technique of Milner, to instill fluid into the peritoneal cavity, leave it for a relatively short "dwell" period and replace with fresh solution (*see* Peers declaration, point 5) and to repeat the process daily. The Peers declaration also noted that the technologies of peritoneal dialysis and adhesion

[1] The reasons of record further include the previously submitted Declaration Under 37 C.F.R. §1.132 of Elizabeth Peers, MA, PhD (hereinafter, "Peers declaration").

reduction are not interchangeable (point 6) at least because the patient requirements are so disparate. The renal failure patient requires the removal of waste and toxins from the body cavity whereas it has been shown that a post-operative patient requires a volume of aqueous solution in the body cavity to prevent tissues adhering together when there is the greatest chance of adhesion formation occurring, i.e., over the at least 2 days first following a surgical procedure.

What is at issue is that neither document provides the following teachings:

1. ***single instillate***; or

2. ***leaving the single instillate in the body for at least 2 days***.

Both these aspects have been argued before extensively, and in particular, in the Peers Declaration under points 5, 6 and 7 and Tab 2 slides 1-3. Taking the missing recitation of a **single instillate**, Milner discusses a minimal daily administration of 3 separate instillations and respective withdrawals rather than a single "one-off" instillate which remains in the body cavity.

Milner states:

> The mode of use of the dialysis solution according to the invention is similar to that of known dialysis solutions. The solution is infused into the peritoneum and allowed to remain there for a predetermined time, after which it is withdrawn and replaced by fresh solution.

Milner, Col. 11, line 1-5 (emphasis added).

The predetermined time (or "dwell time") would be that known to the person of ordinary skill just as stated above and as addressed previously in the Peers declaration. In Milner, dwells of between 3h (col 17, line 6); 6h (col 23, line 52); and up to 12h (col 29, line 36) were specified. Glucose polymer solutions were removed in accordance with normal dialysis practice– Indeed, they would have to be as these were dialysis patients. Milner provides no teaching of providing a single "one off" instillation of an aqueous solution into a body cavity.

Regarding, the second missing recitation in the method of the claimed invention (i.e., leaving the aqueous solution in the body cavity for at least 2 days), the glucose polymer mixture of Milner is only ever "retained" (if one can even call it that because dirty fluid is replaced with clean fluid) for up to 12 hours. This procedure represents, at most, one-quarter

of the time of the minimal instillation period of "at least 2 days" as claimed in the present application, and therefore, the Milner procedure misses the critical period over which adhesion formation is instigated.

Even if, as the Examiner is suggesting, one of ordinary skill in the art is motivated to combine Dobbie and Milner, the resultant method would be either to leave the glucose polymer mixture in the body for up to 12 hours or less and to then withdraw the mixture, or alternatively, if the fluid were not withdrawn, to continue introducing the glucose polymer mixture at regular intervals causing the body cavity to bulge (*see* Peers declaration, point 6). A period of 12 hours does not cover the critical post-operative adhesion formation period, and continuing to introduce the glucose polymer mixture to the patient will lead to abdominal bulging leaving the clinician with the option of the up to 12 hour protocol in view of the cited references and dialysis protocol. Accordingly, the resultant method from the combination of Dobbie and Milner still would be missing critical recitations, i.e., a single instillation and at least 2 days of the aqueous solution remaining in the body cavity.

Applicant respectfully submits that the Examiner has selectively mixed the clinical requirements from different patient groups (dialysis patients and post-operative patients) to construe the prior art to fit the presently claimed invention. While permissible to rely upon selective teachings, it is not permissible to pick and choose the teachings without consideration of each teaching as a whole that, when so considered, clearly do not lead one of ordinary skill in the art to the present invention.

B. Dobbie in view of Treutner

The Examiner acknowledges on page 6 of the Office Action dated July 16, 2007 (hereinafter, "July 2007 Office Action") that Dobbie is "based on what is known from its use in peritoneal dialysis" and indeed emphasizes the point. In contrast to the Examiner's assertions on page 6 of the July 2007 Office Action, Treutner does not (see below for further discussion) teach or suggest a general method for the instillation and does not teach that "the products are instilled and remain" as suggested by the Examiner. Treutner provides no evidence of this assertion. The products as discussed in Treutner are administered, and then the cavity is checked 10 days later. Treutner is silent as to whether there is any product in the cavity at any time point– this is purely speculation by the Examiner.

It is an important point to note, and one not discussed previously, that the 10-day period in Treutner is merely an experimental convenience and is consistent with the animal model that Treutner developed previously, i.e., reference 18 of the present Treutner citation (Treutner et al. *Res. Surg.* 4:50 (1992)). In this previous work, an animal model of post-operative intra-abdominal adhesions was established, and 10 days merely represents a convenient time point when adhesions would have formed and consolidated and the maximum spread of adhesions with sufficient consolidation could be recorded. In neither the present Treutner citation nor in the previously referenced Treutner work did these investigators consider whether the adhesion prevention agents that were administered were indeed still present in the peritoneal cavity at any time point.

The Examiner's entire rationale for the rejection is based on the use by Treutner of a single intraperitoneal administration of each of the test substances and the selection of a 10 day period between administration and determination of adhesion formation (lines 20-21 of the Treutner abstract and the Final Action, page 3, line 14-17): "Ten days later the extent of the adhesions was quantified by morphometry." This step is the methodology of the experiment, using a previously developed animal model of adhesion formation (and cited by Treutner et al., see citation above). What Treutner is doing is allowing a sufficient period to elapse before sacrificing the animals and assessing adhesion formation. Treutner therefore used a suitable period after administration of the test substances and did not draw the conclusion that the substances had to be present for a particular period. Therefore, when the Examiner states, "One of ordinary skill in this art in view of the Treutner et al reference would also know the length of time needed for the solution to remain in the body cavity to be effective" (Final Action, page 3), the Examiner is incorrect.

Treutner is eloquent in the Introduction section regarding the nature, formation and seriousness of adhesions. As ordinarily skilled artisans, at a minimum, the investigators in Treutner would have understood the need to sequentially sacrifice a number of the animals over a period of days if they wished to determine the time for a treatment to have an effect. The investigators would also have known that they would need to compare the pharmacokinetics of the compounds in the peritoneal cavity versus the differences in effectiveness. Treutner does not address this point, and it is the Examiner who is making this

assumption.

Further concerning the deficiencies of Treutner, it is simply not possible to be able to assert that any of the compounds tested in Treutner were the following:

(i) a solution in the body cavity that remains in the body cavity for at least two days; or

(ii) acted as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissue which might otherwise adhere together.

What can be said about the compounds tested in Treutner and possible residency times is the following:

> Turning to Treutner, "The dry substance was dissolved in normal saline for 24hr and the pH was adjusted to 7.45 by sodium phosphate buffer shortly before administration." Treutner, page 765, col 2, para 2. (emphasis added). This means that each of the compounds was administered in saline solution (1ml per 100g body weight) and thereafter approximately 30ml administered where "mean body weight of 3074g ± 20 g." Referring to Table 1, compounds taurolidine (T), phosphatidylcholine(PC), hyaluronic acid (HA), sphingolipid (SL) and galactolipid (GL) are all given as "mg" and hence are dry substances. All these compounds must have been dissolved, suspended or emulsified in saline.
>
> Saline is known to be lost rapidly from the peritoneal cavity within 24h as evidenced from the graph of Tab 4 of the Peers Declaration. Accordingly, any of the dry compounds dissolved directly in saline, i.e., the solids T, PC, HA, SL and GL would not have been in solution in the body cavity 2 days after administration.

Considering the individual compounds, one of ordinary skill in the art is apprised that T is rapidly transported from the peritoneum to the blood by lymphatic absorption. One of ordinary skill in the art would also expect that the enzyme-based agents tested, plasmin and deoxyribonuclease (PD) and streptokinase and streptodornase (SS), would be rapidly absorbed across the peritoneal membrane. One of ordinary skill in the art would also know that the lipids and HA used in Treutner form "coatings" or "lubricant layers" when *in situ* (as stated in Treutner) and as such are not a solution in the body cavity that remains for at least two days as recited in the pending claims. Furthermore, it is Applicant's understanding that tetrachlorodecaoxide (TCDO) like all of the compounds above would have been constituted to a constant volume of 1ml/100g body weight in saline, and it is highly unlikely given the rapid disappearance of saline from the body cavity that it would be in solution in the body

cavity at least 2 days after administration.

As none of the compounds in Treutner are in solution in the body cavity at least two days after administration, they cannot possibly satisfy another recitation of the pending claims, namely that they act as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other, and provide an aqueous formulation as a solution remaining in the body cavity for at least 2 days.

Finally, Treutner teaches away from using a single dose of an adhesion prevention agent. Treutner in the last sentence advocates that TCDO is the most promising candidate as an adhesion prevention agent. Reviewing Table 2 of Treutner, there is the greatest weight loss and a significant weight loss ($p < 0.01$) for the TCDO group. Linking this observation to Figure 1 and reduced adhesions, TCDO is the compound showing the most significantly reduced adhesions. Clearly, since TCDO is the most effective agent at reducing adhesions, the weight loss is attributable not to adhesions but some other toxic effect. "[T]*here is a correlation between the extent of adhesions and the weight loss.*" Treutner, page 770, col 2, para 3. It is well known that weight loss, especially in animals, is associated with toxicity. A toxicologist reviewing this data may conclude that while TCDO is effective at reducing adhesion formation, there are serious toxicological issues arising from a single administration. Thus, a skilled toxicologist would recognize that the dosing regimen and/or route of administration would need to be altered and a single administration would not be appropriate.

Accordingly, Treutner also teaches away from providing a single administration because Treutner shows that effective adhesion reduction may be associated with toxicity; a clearly undesirable effect.

II. Objective Indicia of Unobviousness/Secondary Considerations

Assuming, *arguendo*, that a *prima facie* case of obviousness has been established, Applicant offers further secondary considerations that rebut the *prima facie* case. Such secondary considerations include evidence of commercial success and long-felt needs. *See* Manual of Patent Examining Procedure (MPEP) §716.01(a). Moreover, it is well established that evidence of commercial success can be strong evidence that the invention was not obvious to those skilled in the art at the time the invention was made. *See In re Tiffin*, 443 F.2d 394, 398, 170 USPQ 88, 91 (CCPA 1971). Additionally, licenses of the claimed subject matter may constitute evidence of commercial success, and thus of non-obviousness. *See In re GPAC*, Inc. 57 F.3d at 1580, 35 USPQ 2d at 1122.

The attached Declaration Under 37 C.F.R. §1.132 of Andrew Barrett (hereinafter, "Barrett declaration") provides evidence of such secondary considerations. Mr. Barrett is the Director of Business Development and Licensing for Innovata Limited/ Vectura Group plc, and he has been involved with the present technology, and in particular, an embodiment of the technology provided under the trade name Adept® since the present application was filed. Mr. Barrett was responsible for the UK launch of Adept® in May 2000 and subsequent licensing of European-wide rights of Adept® to Shire Pharmaceuticals in October 2001 and for the re-licensing of Adept® on a global basis to Baxter Healthcare Corporation in 2006. As discussed in detail in the Barrett declaration, Adept® clearly has fulfilled a long-felt surgical need as a safe, efficient, cost-effective, easy to use adhesion reduction agent, and Adept® has proven to be a commercial success.

In conclusion, Applicant respectfully submits that the remarks presented herein address the issue of obviousness in view of the combination of Dobbie and Milner or Treutner, and the secondary considerations previously made of record and newly discussed herein further support the nonobviousness of the present invention to the scientific and medical community in general. Therefore, Applicant respectfully submits that the pending claims are patentable.

Accordingly, Applicant submits that the present application is in condition for allowance and the same is earnestly solicited. The Examiner is encouraged to telephone the undersigned at 919-854-1400 for resolution of any outstanding issues.

Respectfully submitted,

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Betty-Lou Rosser